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EXAMINER	
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ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/520,341	LIU ET AL.	
	Examiner	Art Unit	
	WU-CHENG Winston SHEN	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *1/14/2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-60* is/are pending in the application.

4a) Of the above claim(s) *5-60* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 January 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response received on 01/14/2008 has been entered. Claims 1-60 are pending. Claims 1-4 are amended

Claims 5-60 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim.

Claims 1-4 are currently under examination.

Claim Objections

1. Previous objection of claim 4 is ***withdrawn***.

Claim 4 has been amended to recite "wherein the polypeptide is modified to be in detectably labeled form", which specifically relates back to the polypeptide.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

2. Previous rejection of claims 2, 3, and 4 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is ***withdrawn*** because the claims have been amended.

Claim 2 is amended at part (b) to recite 95% rather than 90% sequence identity. Claim 2 is further amended by deletion of parts (d) and (e) and has been converted to a Markush-type format.

Claim 3 is amended to recite "the polypeptide is a human heparan sulfate 3-O-sulfotransferase 5 polypeptide" rather than the polypeptide "comprises" a human heparan sulfate 3-O-sulfotransferase-5 polypeptide.

Claim 4 is amended such that the use of the term "modified" is specifically recited to relate back to the polypeptide

Claim Rejection - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written description

3. Claims 1-4 as amended remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant's arguments filed 01/14/2008 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 4-9 of the office action mailed on 07/12/2007.

For clarity and completeness of this office action, previous rejection for the reasons of record advanced on pages 4-9 of the office action mailed on 07/12/2007 is summarized below.

Claim 1 is drawn to mutated, and allelic variants of an isolated and purified biologically active heparan sulfate 3-*O*-sulfotransferase-5 polypeptide having greater than 95% sequence identity to SEQ ID No: 2. Claim 2 is drawn to fragments, mutated, and allelic variants of an isolated and purified biologically active heparan sulfate 3-*O*-sulfotransferase-5 polypeptide, while claims 3 and 4 are drawn to human heparan sulfate 3-*O*-sulfotransferase polypeptide, and labeled from of heparan sulfate 3-*O*-sulfotransferase polypeptide respectively. *At the time of filing, only heparan sulfate 3-O-sulfotransferase 5 polypeptide isolated from human was disclosed. The claims do not set forth any structural requirements for biologically active heparan sulfate 3-O-sulfotransferase-5 polypeptide, including the amino acid residues required for the enzymatic activity.* When the claims are analyzed in light of the specification, the invention encompasses a genus of polypeptide molecules encoded by enormous number nucleotide molecules, which are *as yet undisclosed or undiscovered.* The specification teaches the 3-OST-5 polypeptide isolated from human placenta cDNA library, but fails to teach any fragments (encompassed by claim 2), variants (encompassed by claims 1 and 2) or nucleic acids that hybridize to a nucleic acid encoding 3-OST-5 that would have the same functional characteristics as the 3-OST-5 polypeptide disclosed in the specification (SEQ ID NO:2).

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In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been disclosed. The instant specification teaches human 3-*O*ST-5 (SEQ ID NO 2), and no other species encompassed by the genus of 3-OST-5 fragments or variants encompassed by the claims.

Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (e.g. other nucleotide sequences or positions with in a specific gene or nucleic acid), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case the specification only provides putative structural limitation required for being a 3-*O*ST via indication of conserved amino acid residues by the alignment of human 3-*O*ST-5 (SEQ ID NO 2), and 3-*O*ST-1, 3-*O*ST-3A, and 3-*O*ST-3B (SEQ ID Nos 3, 4 and 5). However, there is no information disclosed in the specification regarding polypeptide comprising the amino acid residues required for the enzymatic activity and the nucleic acid encoding the required amino acid residues. There is no evidence on the record of a relationship between the structures of the nucleotide sequences coding for the 3-OST-5 variants or fragments encompassed by claim 2 and the nucleotide sequence set forth by SEQ ID NO: 2 that would provide any reliable information about the structure of polypeptide molecules within the genus. The claimed invention as a whole is not adequately described if the claims require essential or critical elements that are not adequately described in the specification and that is not conventional in the art as of applicants effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641,1646 (1998). The claims read in light of the specification encompass any nucleic acid molecule encoding any polypeptides with detectable 3-*O*ST-5 enzymatic activity as assayed by incubating different fractions separated from Heparin-Sepharose chromatography with medium from cells

as starting material for purification of 3-*O*ST-5 with unlabeled heparin sulfate (HS) and [^{35}S] PAPS to generate [^{35}S] HS *in vitro* (see paragraph [0036]).

In the instant application, the provided information regarding nucleic acid SEQ ID No: 1 (1041 nucleotides which encodes SEQ ID No: 2), SEQ ID No: 2 (346 amino acid residues), and SEQ ID NOs 3, 4 and 5 (corresponding to 3-*O*ST-1, 3-*O*ST-3A, and 3-*O*ST-3B), do not constitute an adequate written description of the broad subject matter of the claims, and so one of skill in the art cannot envision the detailed chemical structure of the polypeptides encoded by nucleic acids encompassed by the claimed heparan sulfate 3-*O*-sulfotransferase polypeptide. Adequate written description requires more than a statement that nucleic acids and polypeptides with a particular quality are part of the invention and reference to a potential method for their identification. The nucleic acid and polypeptide sequences are required.

In conclusion, the limited information provided regarding heparan sulfate 3-*O*-sulfotransferase polypeptide encoded by nucleic acid is not deemed sufficient to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Thus, having considered the breadth of the claims and the provisions of the specification, it is concluded that the specification does not provide adequate written description for the claims.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of

ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

The skilled artisan cannot envision the detailed chemical structure of the encompassed [nucleic acids, polymorphisms, amino acids, etc, use what is appropriate for the situation] regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993), and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. The current situation is a definition of the compound solely based on its functional utility, as a polymorphism, without any definition of the particular polymorphisms claimed.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that, "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

Applicant's arguments and Response to Applicant's Arguments

(i) Applicant argues that Applicant provides a full description of the 3-OST-5 polypeptide of SEQ ID NO 2, conveying to the skilled artisan that they were in possession of the 3-OST-5 polypeptide of SEQ ID NO 2. Further, Applicants also convey with this information that they were in possession of all nucleic acids encoding the 3-OST-5 polypeptide of SEQ ID NO 2.

In response: The Examiner agrees that at the time the application was filed, Applicant had possession of the full length of 3-OST-5 polypeptide as set forth in SEQ ID NO 2, and full length of SEQ ID NO 1, which encodes full length of SEQ ID NO 2.

(ii) Applicant argues that Applicant conveys to the skilled artisan that they were in possession of a genus of biologically active 3-OST-5 polypeptides having greater than 95% sequence identity to SEQ ID NO 2, encoded by a nucleic acid sequence having greater than 95% sequence identity to SEQ ID NO 1 or encoded by a nucleic acid molecule capable of hybridizing under stringent conditions to a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO 1, or a complement thereof.

Applicant argues that Applicant provides a detailed description of the functional characteristics of 3-OST-5 polypeptides. Functional assays for 3-OST-5 polypeptide activity are provided in the specification at the Examples in the form of details for determining the substrate specificity and biological activities of 3-OST-5 isozymes. The Examples describe the differences in activity between the 3-OST-1, 3-OST-3 and 3-OST-5 isozymes. For example, the differences in binding to HSV-1 glycoprotein D (gD) and antithrombin (AT) of heparin sulfate (HS) modified by each of the 3-OST-1, 3-OST-3 and 3-OST-5 isozymes are shown in Tables 3 and 7. The differences in the HS products resulting from enzymatic modification by each of the 3-OST-1, 3-OST-3 and 3-OST-5 isozymes and the differences in biological activity of the various products formed are shown in Table 4. Accordingly, Applicant argues that the specification provides assays for selectively measuring 3-OST-5 isozyme activity, for example, by measuring the HS products formed by 3-OST-5 (3-OST-5 produces IdoUA2S- AnMan3S, GlcUA-AnMan3S6S, and IdoUA2S-AnMan3S6S whereas 3-OST-3 produces IdoUA2S-AnMan3S and IdoUA2S-AnMan3S6S and 3-OST-1 produces GlcUA-AnMan3S6S) or by measuring the binding of HS modified by 3-OST-5 to AT and gD (3-OST-5-modified HS binds to AT and gD whereas 3-OST-l-modified HS binds preferably to AT and 3-OST-3-modified HS binds preferably to gD).

Applicant argues that in addition to measurable functional characteristics, Applicants provides identifying structural characteristics of the genus of biologically active 3-OST-5 isozymes. Specifically, Applicants provide that the genus of polypeptides have greater than 95% sequence identity with SEQ ID NO 2, be encoded by a nucleic acid sequence having greater than

95% sequence identity to SEQ ID NO 1 or be encoded by a nucleic acid molecule capable of hybridizing under stringent conditions to a nucleic acid molecule of SEQ ID NO 1.

Applicant argues that in view of the known correlation between protein structure and function, it reasonably follows that structurally similar proteins are also functionally related. The protein structure-function relationship can be illustrated by the 3-OST isozymes in the instant case. For example, the 3-OST-1, 3-OST-3 and 3-OST-5 isozymes have similar activities in that they all attach sulfate to heparin sulfate. However, the isozymes show differences in substrate preference, which manifests in different biological functions. See, for example, the specification at pages 16-17, lines 28-32 and 1-10, respectively. The 3-OST-1 and 3-OST-3 isozymes are 72% and 58% identical, respectively, to the 3-OST-5 isozyme in the sulfotransferase domain. See, Instant Specification, page 16, lines 14-16. Applicant argues that given that the 3-OST-1 and 3-OST-3 isozymes have similar activity to 3-OST-5 but a relatively low degree of sequence identity (72% and 58%, respectively), the claimed genus of polypeptides having greater than 95% sequence identity to 3-OST-5 can be expected to have even greater functional similarity.

In response: Applicant's arguments have been fully considered and they are not persuasive. The Examiner agrees that the specification provides information regarding distinction between enzymatic activity of isozymes 3-OST-1, 3-OST-3, and 3-OST-5 (3-OST-5 produces IdoUA2S- AnMan3S, GlcUA-AnMan3S6S, and IdoUA2S-AnMan3S6S whereas 3-OST-3 produces IdoUA2S-AnMan3S and IdoUA2S-AnMan3S6S and 3-OST-1 produces GlcUA-AnMan3S6S), the differences between enzymatic activity of isozymes 3-OST-1, 3-OST-3, and 3-OST-5 in binding to HSV-1 glycoprotein D (gD), and the alignment of these isozymes

indicates 3-OST-1 and 3-OST-3 isozymes are 72% and 58% identical, respectively, to the 3-OST-5 isozyme in the sulfotransferase domain. The rejection is maintained because the claims as amended continue to read on any fragment of SEQ ID No: 1 and any fragment of SEQ ID No: 2 as well as any variants that differ in structure by up to 5%. The important information missing to suffice the broad genus as claimed is the demonstration of the domain structure required for the binding to the substrate of the 3-OST-5, and the domain structure required for the binding to the HSV-1 glycoprotein D (gD) of the 3-OST-5. This is particularly critical in instant application because 3-OST-1, 3-OST-3, and 3-OST-5 share low degree of homology, and the specification points out that the substrate specificity of 3-OST isoforms is determined by the three-dimensional structure (i.e. tertiary structure) of the enzymes, See page 16 lines 14-20, cited on second paragraph of page 17 of the response filed by Applicant on 01/14/2008. Mere alignment of amino acid sequences (i.e. primary structure) between 3-OST-1, 3-OST-3, and 3-OST-5 for identification of putative sulfotranferase domain is not sufficient to meet the requirement for written description. Additionally, the isoforms 3-OST-1, 3-OST-3, and 3-OST-5 are not encoded by the same gene. Accordingly, the specification only discloses cDNA encoding 3-OST-5 from human placenta. Furthermore, the specification does not provide any structure of 3-OST-5 required for the binding to the HSV-1 glycoprotein D (gD), which is encompassed by the broad genus of the biological activity of 3-OST-5 polypeptide. It is also noted that the specification only discloses the isolation of human 3-OST-5 isozyme, no 3-OST-5 isozyme has been identified from any other mammalian species.

As stated in the rejection dated 07/12/2008 and reiterated in this office action, at the time of filing, only heparan sulfate 3-O-sulfotransferase 5 polypeptide isolated from human placenta

was disclosed. The claims do not set forth any structural requirements for biologically active heparan sulfate 3-O-sulfotransferase-5 polypeptide, including the amino acid residues required for the biological activity. Based on the abovementioned discussions, it is determined that at the time the application was filed, Applicant had possession of the full length of 3-OST-5 polypeptide as set forth in SEQ ID NO 2, and full length of SEQ ID NO 1, which encodes full length of SEQ ID NO 2. Applicant is directed to Example 11 A of Revised Written Description Guidance posed 03/25/08 via http://www.uspto.gov/web/menu/written.pdf

The Examiner notes that the case laws *Enzo* Court (pages 16-17 of the response) and *Adler* case (page 18 of the response) cited by Applicant cannot be applied to the instant application because the status of art of the subject matters are different. Specifically, in instant application, various biological activities residing in different fragments or variants encompassed by the broad genus of 3-OST-5 polypeptide are determined by the three-dimensional structure (i.e. tertiary structure) of the enzymes. Therefore, the specification fails to provide correlation between structure and function of fragments encompassed by the broad genus of 3-OST-5 polypeptide.

Scope of Enablement

4. Claims 1-4 as amended remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated and purified biologically active heparan sulfate 3-*O*-sulfotransferase 5 polypeptide wherein the polypeptide catalyzes the reactions generating at least three 3-O-sulfated disaccharides as follows: IdoUA2-AnMan3S, GlcUA-

AnMan3S6S, and IdoUA2S-AnMan3S6S, **does not** reasonably provide enablement for (1) any fragment or variant of polypeptide encoded by a nucleic acid sequence as set forth in SEQ ID NO 1; (2) any fragment of a polypeptide encoded by a nucleic acid sequence having greater than 95% but less than 100% sequence identity of SEQ ID No 1; (3) any fragment of polypeptide having an amino acid sequence having greater than 95% sequence identity of SEQ ID NO 2; or (4) any polypeptide encoded by a nucleic acid molecule capable of hybridizing under stringent conditions to a nucleic acid molecule comprising the nucleotides of SEQ ID NO 1, or a complement thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to a make or use the invention commensurate in scope with these claims. Applicant's arguments filed 01/14/2008 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 9-14 of the office action mailed on 07/12/2007. The scope of enablement has revised to reflect the claim amendment reciting "having greater than 95%" instead of reciting "having greater than 90%".

Previous rejection on the aspects regarding any fragments of polypeptide which is a biological equivalent of the polypeptide set forth in SEQ ID NO 2 (which corresponded to deleted limitation of claim 2 (d)); any fragment of a polypeptide which is immunologically cross-reactive with an antibody which is immunoreactive with a polypeptide comprising part or all of the amino acids of SEQ ID NO 2 (which corresponded to deleted limitation of claim 2 (e)), is **moot** because claim 2 has been amended and these limitations of claim 2 have been deleted.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as

routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a prima facie case is discussed below.

Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

For clarity and completeness of this office action, previous rejection for the reasons of record advanced on pages 9-14 of the office action mailed on 07/12/2007 is summarized below.

The nature of the instant invention is an isolated and purified biologically active heparan sulfate 3-*O*-sulfotransferase-5 (isoform) polypeptide. The breadth of the claims, in light of specification, encompasses isolated and purified biologically active heparan sulfate 3-*O*-sulfotransferase 5 polypeptides.

The specification disclosed the terms "3-*O*ST-5 gene product", "3-*O*ST-5 protein", and "3-*O*ST-5 polypeptide" also include analogs of HS D-glucosaminyl-3-*O*-sulfotransferase

isoform 5 molecules and further defines analogs at paragraph [0067], US PGPUB 2006/0165673, publication of instant application. The specification states that there is no need for a "3-*O*ST-5 gene product", "3-*O*ST-5 protein", and "3-*O*ST-5 polypeptide" to comprise all or substantially all of the amino acid sequence of a native 3-*O*ST-5 gene product. Shorter or longer sequences are anticipated to be of use in the invention. Thus, the terms "3-*O*ST-5 gene product", "3-*O*ST-5 protein", and "3-*O*ST-5 polypeptide" also include fusion or recombinant HS D-glucosaminyl-3-*O*-sulfotransferase isoform 5 polypeptides and proteins comprising sequences of the present invention (See (paragraph [0067]). The specification also disclosed a multiple amino acid sequence alignment of human 3-*O*ST-5 (SEQ ID NO 2) with human 3-*O*ST-1, 3-*O*ST-3A, and 3-*O*ST-3B (SEQ ID Nos 3, 4 and 5, respectively) in Figure 2 (See paragraph [0029]), and that the activity of 3-OST-5 was monitored by incubating the eluent (10 µl) with unlabeled heparin sulfate (HS) and [^{35}S] PAPS to generate [^{35}S] HS. It is noted that PAPS is a coenzyme of 3-*O*ST enzymes, which stands for 3'-phosphoadenosine 5'-phosphosulfate (See paragraph [0036]).

With regard to lack of enablement support for (1) any fragment or variant of polypeptide encoded by a nucleic acid sequence as set forth in SEQ ID NO 1, (2) any fragment of a polypeptide encoded by a nucleic acid sequence having greater than 95% sequence identity of SEQ ID No 1, (3) any fragments of polypeptide having an amino acid sequence having greater than 95% sequence identity SEQ ID NO 2, it is noted that the specification does not provide any working example other than full length of SEQ ID No 2 (346 amino acid residues) being biologically active as an 3-*O*ST enzyme (Examples 7- 9 of instant application). Accordingly, for an artisan to use or make the instantly claimed functional fragments or functional equivalent

variants, an artisan would first have to identify if the sequences had 3-OST enzymatic activity. Claim 1 encompasses allelic variants of an isolated and purified biologically active heparan sulfate 3-*O*-sulfotransferase-5 polypeptide having greater than 95% sequence identity to SEQ ID No: 2. Claim 2 encompasses nucleic acid encoding fragments having greater than 95% sequence identity to SEQ ID NO: 2, which include fragments as small as a peptide consisting of 20 amino acid residues. Claim 2 also encompasses nucleic acids with greater than 95% sequence identity to SEQ ID No: 1, which include fragments as small as an oligonucleotide consisting of 20 nucleotides. The level of experimentation to determine which of the fragments or variants would encode 3-OST-5 biological activities would be undue.

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Also since the functional domain necessary and sufficient for the 3-*O*ST-5 biological activity is not disclosed, an artisan would not know which sequences would need to be conserved in a biological activity of SEQ ID NO: 2 to render the equivalent biological function as claimed. An artisan would not know which 5% of the sequence could be different from any fragment of the polypeptide sequence of SEQ ID NO: 2 and still retain the function of the claimed 3-OST-5 biological activity. Therefore, an artisan would not know how to make a biological active polypeptide encoded by any fragment of the nucleic acid having greater than 95% sequence identity to nucleotides 1-1041 of SEQ ID NO: 1.

Therefore, given that the specification and art lack specific guidance to the necessary and sufficient functional domain of the 3-*O*ST-5 enzyme disclosed, an artisan would have to do further in vitro studies to determine which part of the sequence are the necessary and sufficient functional domain of the 3-*O*ST-5 enzyme and this level of empirical experimentation would be considered undue.

The instant invention is also drawn to any polypeptide encoded by a nucleic acid molecule capable of hybridizing under stringent conditions to a nucleic acid molecule comprising the nucleotides of SEQ ID NO 1, or a complement thereof. However, the state of the art suggests that sequences identified by their hybridization properties are unpredictable in their identity in sequence to the original sequence to which it hybridized. **Kennell** (Principles and practices of nucleic acid hybridization. *Prog Nucleic Acid Res Mol Biol.* 11:259-301, 1971) teaches that 25 to 50% nucleic acid identity is all that is necessary for hybridization of a sequence under any conditions and that obtaining non-specific hybridization products are highly common in the art (par bridging p. 260 and 261 and par 1 of p. 261). The specification provides general guidelines and conditions for obtaining hybridization products. However, these conditions are exemplary and not limiting. Furthermore, these general guidelines and conditions provided by the specification do not provide any guidance to overcome the unpredictabilities described in the art. Therefore, an artisan would not know if a sequence that hybridized to the nucleotides of 1-1041 of SEQ ID NO: 1 would be a true complementary sequence capable of encoding a 3-OST enzyme or a non-specific hybridization product. Furthermore, for an artisan to use or make the claimed nucleic acid capable of hybridizing to the nucleotides of 1-1401 of SEQ ID NO: 1, they would first have to sequence the product to determine if it was a true complement and then also test the functionality of the nucleotide for its 3-OST enzymatic activity. This level of experimentation would be considered undue. Furthermore, even if a nucleic acid sequence meet the limitations of having greater than 95% sequence identity to the full length of SEQ ID 1 and hybridizes to SEQ ID 1 under exemplary stringent hybridization conditions as disclosed in instant application (See paragraphs [0077]), the nucleic acid sequence

may not have 3-OST biological activity. In this regard, for instance, **Munoz et al.** teach that single point mutations R72A, R67A, and K123A result in 3-*OST*-1 mutants that are inactive (See Figure 3B, and Discussion, bridging paragraph of columns, Munoz et al. Affinity, kinetic, and structural study of the interaction of 3-O-sulfotransferase isoform 1 with heparan sulfate, *Biochemistry*, 45(16): 5122-8, 2006).

In view of the state of the art, the unpredictability in the art, and the lack of specific guidance and working examples in the specification, one of skill in the art would have to perform undue experimentation to make and use the invention commensurate in scope with these claims 1-4 of instant application.

Applicant's arguments and Response to Applicant's Arguments

Applicant argues that the experimentation required to make and use the genus of biologically active 3-OST-5 polypeptides of amended claims 1-4 is not undue, as it is routine in nature. Further, required techniques are well known to the skilled artisan, and/or are disclosed in the instant application. Applicant argues that, for example, in the present case, undue experimentation would not be required to make and use a 3-OST-5 polypeptide having greater than 95% sequence identity to SEQ ID NO 2 or encoded by a nucleic acid molecule capable of hybridizing under stringent conditions to a nucleic acid molecule of SEQ ID NO 1, because amino acid alterations can be made to the proteins having the sequence of SEQ ID NO 2 by standard molecular biological procedures including, for example, oligonucleotide-directed mutagenesis, and procedures for performing stringent hybridizations are well known in the art. Applicant argues that the present disclosure provides the complete sequence of nucleic acids

encoding the protein of SEQ ID NO 2, so the experimentation required to make a mutation to the encoding nucleic acids is routine. In addition, Applicants provide assays to determine whether the modified protein possesses 3-OST-5 activity. See, e.g., Instant Specification, Examples 2-9. Applicant argues that it would be routine for one of ordinary skill in the art to perform the detailed assays provided in the specification for measuring 3-OST-5 activity. Further, Applicant argues that guidance to make the appropriate amino acid modifications is provided by the sequence comparison in Figure 2 showing conserved and less conserved regions between the 3-OST isozymes, 3-OST-1, 3-OST-3A, 3-OST-3B and 3-OST-5.

Applicant argues that the skilled artisan further appreciates that limited amino acid alterations, e.g., a single amino acid modification, generally can be made with a reasonable expectation of maintaining protein function. Gassner et al., Proc. Nat'l Acad. Sci USA 93:12155-58 (1996); Gassner et al reveals that considerable (up to 10) amino acid alterations can be made even to the tightly packed core of a globular protein without eliminating activity or folding of the protein. Wells, Biochemistry 29:8509-17 (1990) discloses that the free energy changes in mutant proteins generally are additive with increasing numbers of amino acid mutations. Wells shows that proteins generally function when they have single, or even multiple, amino acid changes. Applicant argues that, in the present case, as evidenced by Gassner et aL and Wells, for example, the proteins with altered sequences that are encompassed by amended claims 1-4 would be reasonably expected to retain biological function. In any case, Applicant argues that the variant polypeptides without biological activity could be identified with routine experimentation. Along the same line of argument, Applicant cited *Adler* case (page 22 of response) indicating that

mutated sequences, allelic variants of a given polynucleotide can be determined without undue experimentation.

In response: The Examiner agrees with Applicant on the aspect that alteration in amino acid alterations can be made to the proteins having the sequence of SEQ ID NO 2 by standard molecular biological procedures including, for example, oligonucleotide-directed mutagenesis, and procedures for performing stringent hybridizations are well known in the art. The Examiner acknowledges that the sequence comparison in Figure 2 showing conserved and less conserved regions between the 3-OST isozymes, 3-OST-1, 3-OST-3A, 3-OST-3B and 3-OST-5. However, this conservation is not correlated with function because the specification disclose three-dimensional structure is critical for substrate recognition and binding, See paragraph [0059], US PGPUB 2006/0165673, publication of instant application. The Examiner acknowledges that limited amino acid alterations, e.g., a single amino acid modification, can be made with a reasonable expectation of maintaining protein function as demonstrated for T4 lysome reported by Gassner et al. (Appendix A), and for the core of a globular protein reported by Wells et al (Appendix B), and by *Alder* case for a particular bitter taste receptor, however, the specification has not given the appropriate support to delineate where these alterations can occur yet still retain biological activity.

The rejection set forth the claims are not enabled for (1) any fragment or variant of polypeptide encoded by a nucleic acid sequence as set forth in SEQ ID NO 1; (2) any fragment of a polypeptide encoded by a nucleic acid sequence having greater than 95% sequence identity of SEQ ID No 1; (3) any fragment of polypeptide having an amino acid sequence having greater

than 95% sequence identity of SEQ ID NO 2; or (4) any polypeptide encoded by a nucleic acid molecule capable of hybridizing under stringent conditions to a nucleic acid molecule comprising the nucleotides of SEQ ID NO 1, or a complement thereof.

As discussed in the preceding section on response to arguments on written description, in instant application, various biological activities residing in different fragments encompassed by the broad genus of 3-OST-5 polypeptide are determined by the three-dimensional structure (i.e. tertiary structure) of the enzymes. The specification fails to provide correlation between structure and function of fragments encompassed by the broad genus of 3-OST-5 polypeptide. An artisan would not know which 5% of the sequence could be different from any fragment of the polypeptide sequence of SEQ ID NO: 2 and still retain the function of the claimed 3-OST-5 biological activity. An artisan would not know how to make a biological active polypeptide encoded by any fragment of the nucleic acid having greater than 95% sequence identity to nucleotides 1-1041 of SEQ ID NO: 1, or by any nucleic acid molecule capable of hybridizing under stringent conditions to a nucleic acid molecule comprising the nucleotides of SEQ ID NO 1, or a complement thereof.

Therefore, given that the specification and art lack specific guidance to the necessary and sufficient functional domain of the 3-*O*ST-5 polypeptide disclosed, an artisan would have to do further *in vitro* studies to determine which part of the sequence are the necessary and sufficient functional domain of the 3-*O*ST-5 enzyme and this level of empirical experimentation would be considered undue.

Conclusion

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

6. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent

examiner, Peter Paras, can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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